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TITLE: A Nationwide Population-Based Approach to Study Health-Related and Psychosocial Aspects of Neurofibromatosis Type 1

PRINCIPAL INVESTIGATOR: Dr. Jeanette Falck Winther

CONTRACTING ORGANIZATION: Danish Cancer Society Research Center
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**14. ABSTRACT** Using the unique resources for conducting epidemiological research in Denmark, we suggest carrying out seven studies in this research project with the overall objective of evaluating health-related and psychosocial aspects of NF1 in a large population-based setting. Studies 1-5 are register-based studies, study 6 a questionnaire study, and study 7 an interview study.
Within this first year, 1) we accomplished to receive all approvals for this project; i.e., the data approval from the Danish Data Protection Agency, the approval from the local Institutional Review Board (IRB), and the initial approval from HRPO for all register-based studies 1-5, 2) we have prepared for data linkages by updating the *clinical* NF1 study cohort of patients affiliated to the two national Centers for Rare Diseases in Denmark, by preparing a list of variables needed from the respective population-based registries to run the approved register-based studies 1-5, and by sending an request to Statistics Denmark to obtain these data, 3) we have hired a scientific assistant for two years ('to-be-named' in our grant application) to be part of the staff on this project (start Sept 1, 2015), and 4) finally, we have held a kick-off meeting at our research center with participants being all colleagues within the research center involved in this project as well as the three unpaid consultants; i.e., two clinical experts in NF1 from the two Rare Disease Clinics in Denmark and a clinical geneticist with expertise in ethical aspects.

**15. SUBJECT TERMS**
Neurofibromatosis type 1, population-based, nation-wide, clinical epidemiology, somatic disease, mental disease, cohabitation, educational attainment, psychosocial burden, patient-reported outcomes, neuropsychological assessments

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# A NATIONWIDE POPULATION-BASED APPROACH TO STUDY HEALTH-RELATED AND PSYCHOSOCIAL ASPECTS OF NEUROFIBROMATOSIS TYPE 1

## 1. Annual Report July 2015

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## 1. INTRODUCTION

Using the unique resources for conducting epidemiological research in Denmark with personal identification numbers for all citizens and the existence of a number of unique population-based, nationwide administrative registries, we suggest carrying out seven studies with the overall objective of evaluating health-related and psychosocial aspects of NF1 in a large population-based setting. The study cohorts consist of a *clinical* NF1 cohort of patients affiliated to the two national Centers for Rare Diseases (CRD) and a *register-based* cohort of all patients hospitalized for or with existing NF1 in Denmark as well as a large population-based comparison cohort. The specific aims are:

- to screen for somatic (study 1) and psychiatric disease (study 2) throughout the different phases of life as well as to assess the risk of adverse pregnancy outcomes (abortions and stillbirths; study 3) in patients with NF1 in a nationwide population-based setting using large-scale record linkage techniques with national health outcome registers. Health-related outcomes will be documented in retrospective cohort studies of 2484 patients in the combined clinical and register-based NF1 cohort by linkage to nationwide health registries and compared with those in population comparisons

- to measure how patients with NF1 manage the transition from child- into adulthood in a similar approach by determining the following psychosocial and socioeconomic achievements or life goals based on information obtained from national population-based administrative registries: leaving home, cohabitation, and founding a family (study 4) as well as educational attainment (study 5)

- to thoroughly investigate the psychosocial burden (depression, anxiety, quality of life) (study 6) and impairment in cognitive functioning and need for professional support (study 7) among adults with NF1 in the clinical cohort using questionnaire-based patient-reported outcome measures (n=360) and neuro-psychological assessments performed by trained psychologists in a selected sub-sample (n=100)

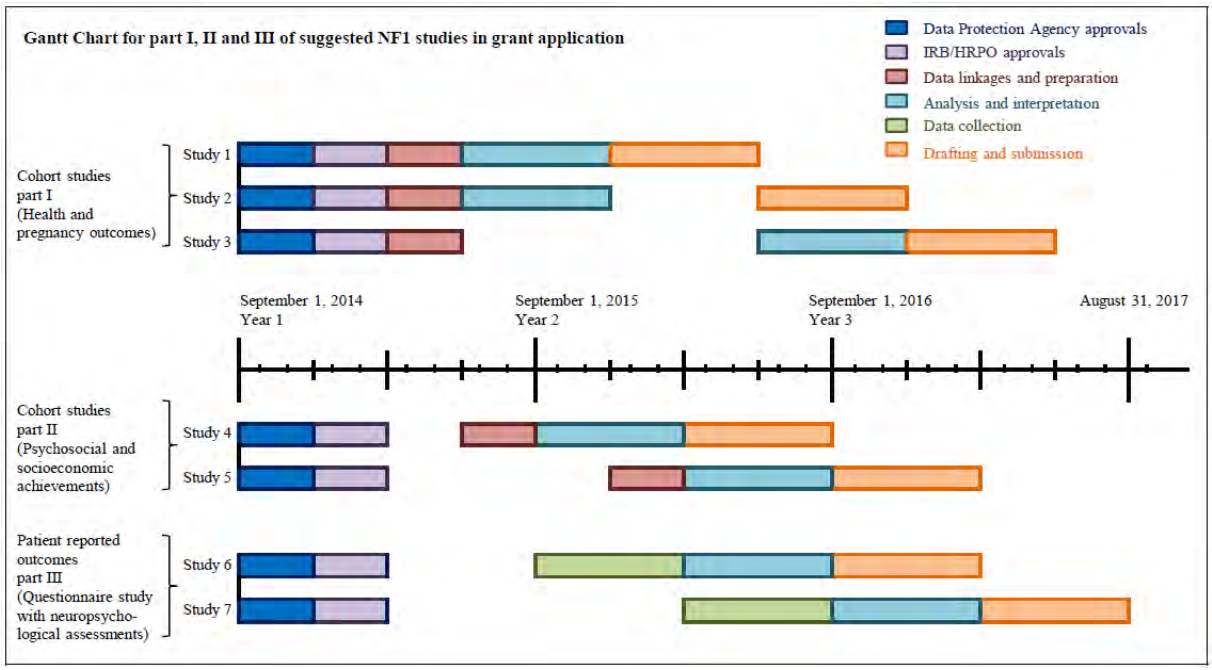
## 2. KEYWORDS

Neurofibromatosis type 1, population-based, nationwide, clinical epidemiology, somatic disease, mental disease, cohabitation, educational attainment, psychosocial burden, patient-reported outcomes, neuropsychological assessments

## 3. ACCOMPLISHMENTS

**Major goals of project**
According to the latest revised version of the SOW with first year estimated to start up September 1 2014 (inserted below; the contract ended up starting July 1), the major goals/tasks for the first year were to:

1) obtain all approvals before starting up the project (study 1-7)
2) to conduct data linkages and prepare for analyses (study 1-4)




**Accomplished under these goals**

**Approvals (referring to point 1 in major goals of project):** within this first year, we accomplished to receive all approvals: i.e.,

- The data approval from the Danish Data Protection Agency (17 July 2014)
- The approval from the local Institutional Review Board (IRB) (23 October 2014)
- The initial approval from HRPO for all register-based studies 1-5, with the following limitation (see highlights below) (19 June 2015):

***SUBJECT:*** *Initial Approval for the Protocol, "A Nationwide Population-Based Approach to Study Health-Related and Psychosocial Aspects of Neurofibromatosis Type 1," Submitted by Jeanette F. Winther, MD, Danish Cancer Society Research Center, Copenhagen, Denmark, Proposal Log Number NF130037, Award Number W81XWH-14-1-0054, HRPO Log Number A-18370.i*

1. *The subject protocol was approved by the Danish Cancer Society Research Center Institutional Review Board (IRB) on 23 October 2014. The US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, US Army, and USAMRMC human subjects protection requirements.*

*2. The USAMRMC ORP HRPO approved this no greater than minimal risk study for the enrollment of approximately 2,500 subjects in the five registry studies.* ***NOTE:*** *Separate HRPO approvals are required for the two additional studies embedded in this protocol, which include the questionnaire-based and patient reported outcome (study 6) and neuro-psychological assessments (study 7).*

**Data linkages (referring to point 2 in major goals of project):** within this first year, we accomplished:

- To update the *clinical* NF1 cohort of patients affiliated to the two national Centers for Rare Diseases (CRD); i.e., we have just received an updated cohort from the State Hospital (Rigshospitalet) in Copenhagen and an updated cohort is being prepared for the project at the Aarhus University Hospital, Skejby

- To prepare a list of variables needed from the respective population-based registries to run the approved register-based studies (studies 1-5)

- To send an request to Statistics Denmark to obtain these data

**Scientific assistant:** Within this year, I have hired a scientific assistant for two years ('to-be-named' in our grant application) to be part of the staff on this project (start Sept 1, 2015). Karoline Doser has a Master in Clinical Pedagogic and Therapeutic Studies from the Catholic University of Applied Sciences Freiburg in Germany. Karoline Doser is fluent in English (travel stipend with a stay in San Francisco, USA) and is now living in Denmark.

**Kick-off meeting:** Finally, I have held a kick-off meeting at our research center (4 May 2015). Participants were all colleagues within the research center involved in this project as well as the three unpaid consultants; i.e., Consultant Hanne Hove and Professor John Rosendahl Østergaard (both experts in familial cancer syndromes including NF1) from the two Rare Disease Clinics at the State hospital (Rigshospitalet) in Copenhagen and the University Hospital Aarhus, Skejby, respectively, and Professor Sven Asger Sørensen (a clinical geneticist with expertise in ethical aspects). At the meeting I gave an overview of the research program and together with my two co-investigators Dr. Dalton and Dr. Bidstrup, we gave a more detailed presentation of the three major parts of this research project:

1) Health and pregnancy outcomes in patients with NF1 (studies 1-3)
2) The transition from child- into adulthood for NF1 patients (studies 4-5), and
3) Studies of the psychosocial burden and cognitive functioning and need for professional support among adults with NF1 (studies 6-7)

**Training and professional development**

*Postdoctoral traineeship*

One-on-one work: Line Kenborg has assisted Dr. Winther (her mentor) in the tasks related to obtaining the permissions and in preparation of variable lists.

Line Kenborg has attended the weekly seminars at the Danish Cancer Society Research Center and she has been organizing journal clubs and teaching younger colleagues and students at these meetings.

**Dissemination to communities of interest**

Nothing to report

**Plan for the next reporting period**
During the next reporting period, analyses will be conducted for studies 1, 2 and 4. A manuscript for study 1 will be drafted and submitted, and the postdoctoral fellow and the scientific assistant will start drafting manuscripts for study 2 and 4.

Another major task will be to prepare information in request for obtaining permission for studies 6-7:
As defined by the "*Danish Act on Research Ethics Review of Health Research Projects*", the project does not constitute a health research project, but is considered a register research project (study 1-5) as well as interview- and questionnaire-based study (studies 6-7). Thus, the Committees on Health Research Ethics for the Capital Region of Denmark will not have to approve these two studies.

Studies 6-7, however, will be needing separate HRPO approvals. Therefore, documents such as invitation letter, information brochure, informed consent forms, and especially questionnaires for this special group of NF1 patients will be developed as part of this research program. When these documents have been drafted, they will be send for HRPO approval. As soon as we have the approval, data collection will start up.

Finally, we will develop a website that gives an overview of ongoing activities within the project and which disseminates the results of the research activities.

## 4. IMPACT
Nothing to report

## 5. CHANGES/PROBLEMS
Nothing to report

## 6. PRODUCTS
Nothing to report

## 7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

**Individuals who have worked on the project**

| | |
|---|---|
| Name: | Jeanette Falck Winther |
| Project Role: | PI |
| Researcher Identifier (e.g. ORCID ID): | ORCID ID: 0000-0002-3440-5108 |
| Nearest person month worked: | 1 |

| | |
|---|---|
| Contribution to Project: | *Dr. Winther has been responsible for obtaining all approvals including obtaining all information in request to obtain permissions and related correspondence* |
| Funding Support: | |

| | |
|---|---|
| Name: | Line Kenborg |
| Project Role: | Postdoctoral fellow |
| Researcher Identifier (e.g. ORCID ID): | - |
| Nearest person month worked: | 1 |
| Contribution to Project: | Line Kenborg has assisted Dr. Winther in tasks related to obtaining approvals and have prepared variable lists for Statistics Denmark |
| Funding Support: | |

**Change in the active other support of PI/key personnel**

Line Kenborg has received the following grant:

*Title:* Neurological late effects in survivors of non-CNS childhood cancer

*Time commitment:* 50% (used for the first half year of this US Army grant while we were waiting for permission to start up this NF1 project)

*Supporting agency:* The Danish Childhood Cancer Foundation

*Address of the funding agencies Grant Officer:* The Danish Childhood Cancer Foundation, Dampfærgevej 22, P.B. 847, DK-2100 Copenhagen, Denmark - no specific grant officer

*Performance period:* January 2015 - December 2015

*Level of funding:* 526.000 DKK; *Role:* PI

*Goals and aims of the study:* To evaluate the risk of treatment-induced neurological disease in non-CNS childhood cancer survivors

**Other organizations involved as partners**
Nothing to report

## 8. SPECIAL REPORTING REQUIREMENTS

Nothing to report

## 9. APPENDICES

None